

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
23 January 2003 (23.01.2003)

PCT

(10) International Publication Number
WO 03/006424 A1(51) International Patent Classification⁷: C07C 233/60, 233/58, 233/59, 233/62, C07D 335/12, A61K 31/185, A61P 35/00, 31/12

(21) International Application Number: PCT/EP01/07948

(22) International Filing Date: 10 July 2001 (10.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant (for all designated States except US): 4SC AG [DE/DE]; Am Klopferspitz 19, 82152 Martinsried (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): KRAMER, Bernd [DE/DE]; Apolloniastr. 56, 52080 Aachen (DE). LEBAN, Johann [AT/DE]; Radolfzellerstr. 9a, 81243 München (AT).

(74) Agent: VIERING, JENTSCHURA & PARTNER; Steinsdorfstr. 6, 80538 München (DE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

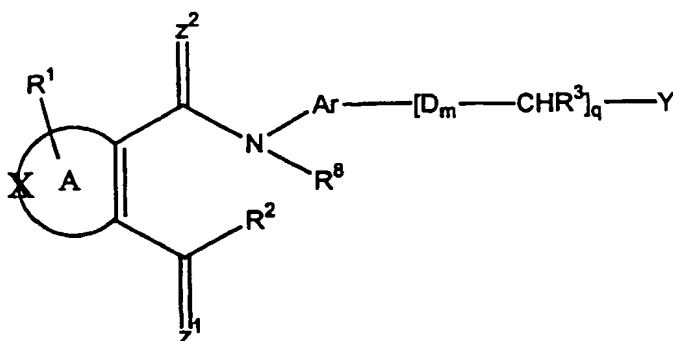
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL COMPOUNDS AS ANTI-INFLAMMATORY, IMMUNOMODULATORY AND ANTI-PROLIFERATORY AGENTS



(I)

(57) Abstract: The present invention relates to compounds of the general formula (I), wherein A is a non-aromatic ring system containing 4 to 8 carbon atoms, wherein the ring system comprises at least one double bond and wherein one or more of the carbon atoms in the ring can be substituted by a group X, wherein X is selected from the group consisting of S, O, N, NH, NHR⁴, SO or SO₂, and wherein one or more of the carbon atoms of the ring can carry a substituent R¹; D is O, S, SO₂, NH, NHR⁴, or CH₂; R¹ is independently H, halogen, CF₃, OCF₃, or C₁-C₃-alkyl;

R² is H, OH, OR⁶, NH₂, NHR⁷; R⁶ is H, alkyl, cycloalkyl, aryl, arylalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical(acyloxy)alkyldiester, dialkylphosphate; R⁷ is H, alkyl, aryl, O-alkyl, O-aryl, cycloalkyl or O-cycloalkyl; R⁸ is hydrogen or alkyl; R³ is H, cycloalkyl, aryl, O-alkyl, O-aryl or O-cycloalkyl; R⁴ is C₁-C₃-alkyl or an unsaturated or saturated carbocycle selected from the group consisting of cyclopentyl, cyclohexyl or aryl; Z¹ and Z² are independent from each other O, S, NH or NR⁵; R⁵ is OH, O-alkyl, O-aryl, alkyl or aryl; Ar is a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring; Y is hydrogen, halogen, CF₃, OCF₃, substituted or unsubstituted alkyl; substituted or unsubstituted cycloalkyl, Ar, O-substituted or unsubstituted Ar, O-substituted or unsubstituted alkylaryl, O-substituted or unsubstituted arylalkyl or (Formula); m is 0 or 1; and q is 0 to 10; with the proviso that when ring A is an unsubstituted carbocycle containing five carbon atoms and one double bond between the CZ¹ and CZ² substituents with Z¹ = Z² = O and R² = OH, the following compounds are excluded: q = 0; Y = hydrogen; Ar = phenylene or naphthylene, phenylene substituted with one or two chlorine atoms or with 2-methyl, 4-methyl, 4-methoxy, 4-ethoxy, 2, 6-diethyl, 2-chloro-4-methyl, 4-bromo, 4-cyano, 2, 3-difluoro, 2, 6-difluoro, 2, 3, 4-trifluoro; q = 0; Y = phenyl; Ar = phenylene; Q = 1; m = 1; R³ = H; Ar = phenylene; Y = 4-chloro-phenyl; D = O, S; q = 1; m = 1; R³ = H; Ar = phenylene; Y = 4-phenyl; D = O.

WO 03/006424 A1

Novel Compounds as Anti-Inflammatory, Immunomodulatory and Anti-Proliferatory Agents

Description

5

The present invention relates to novel compounds that can be used as antiinflammatory, immunomodulatory and antiproliferatory agents. In particular the invention refers to new compounds which inhibit dihydroorotate dehydrogenase (DHODH), a process for their manufacture, pharmaceutical compositions containing them and to their use for the treatment and prevention of diseases, in particular their use in diseases where there is an advantage in inhibiting dihydroorotate dehydrogenase (DHODH).

10

Rheumatoid arthritis (RA) is a disease which is quite common especially among elder people. Its treatment with usual medications as for example non-steroid anti-inflammatory agents is not satisfactory. In view of the increasing ageing of the population, especially in the developed Western countries or in Japan the development of new medications for the treatment of RA is urgently required.

15

WO 99/38846 and EP 0 646 578 disclose compounds which are reported to be useful for treatment of RA.

20

A medicament against rheumatoid arthritis with a new mechanism of action, leflunomide, was recently put on the market by the company Aventis under the tradename ARAVA [EP 780128, WO 97/34600]. Leflunomide has immunomodulatory as well as anti-inflammatory properties [EP 217206, DE 2524924]. The mechanism of action is based upon the inhibition of dihydroorotate dehydrogenase (DHODH), an enzyme of the pyrimidine biosynthesis.

25

In the body, DHODH catalyzes the synthesis of pyrimidines, which are necessary for cell growth. An inhibition of DHODH inhibits the growth of (pathologically) fast proliferating cells, whereas cells which grow at normal speed may obtain their required pyrimidine bases from the normal metabolic cycle. The most important types of cells for the immuno response, the lymphocytes, use exclusively the synthesis of pyrimidines for their growth

30

and react particularly sensitively to DHODH inhibition. Substances that inhibit the growth of lymphocytes are important medicaments for the treatment of auto-immuno diseases.

5 The DHODH inhibiting leflunomide (ARAVA) is the first medicament of this class of compounds (leflunomides) for the treatment of rheumatoid arthritis. WO 99/45926 is a further reference that discloses compounds which act as inhibitors of DHODH.

10 JP-A-50-121428 discloses N-substituted cyclopentene-1,2-dicarboxylic acid monoamides as herbicides and their syntheses. For example, N-(4-chlorophenyl)-1-cyclopentene-1,2-dicarboxylic acid monoamide is produced by reacting 1-cyclopentene-1,2-dicarboxylic anhydride with 4-chloroaniline.

15 In the Journal of Med. Chemistry, 1999, Vol. 42, pages 3308-3314, virtual combinatorial syntheses and computational screening of new potential Anti-Herpes compounds are described. In Table 3 on page 3313 experimental results regarding IC₅₀ and cytotoxicity are presented for 2-(2,3-difluorophenylcarbamoyl)-1-cyclopentene-1-carboxylic acid, 2-(2,6-difluorophenylcarbamoyl)-1-cyclopentene-1-carboxylic acid and 2-(2,3,4-trifluorophenylcarbamoyl)-1-cyclopentene-1-carboxylic acid.

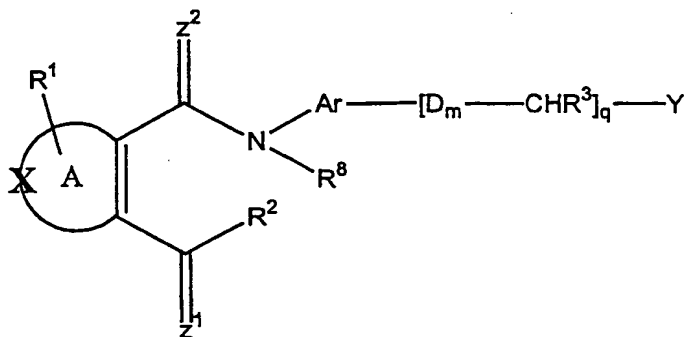
20 It is an object of the present invention to provide alternative effective agents which can be used for the treatment of diseases which require the inhibition of DHODH.

Accordingly, a novel class of compounds with an anti-inhibitory effect on DHODH, in particular human DHODH, was found.

25

30

The present invention is therefore directed to compounds of the general formula (I)



wherein

A is a non-aromatic ring system containing 4 to 8 carbon atoms, wherein the ring system comprises at least one double bond and wherein one or more of the carbon atoms in the ring can be substituted by a group X, wherein X is selected from the group consisting of S, O, N, NH, NHR^4 , SO or SO_2 , and wherein one or more of the carbon atoms of the ring can carry a substituent R^1

D is O, S, SO_2 , NH, NHR^4 , or CH_2 ,

R^1 is independently H, halogen, CF_3 , OCF_3 or $\text{C}_1\text{-C}_5\text{-alkyl}$;

R^2 is H, OH, OR^6 , NH_2 , NHR^7 ;

R^6 is H, alkyl, cycloalkyl, aryl, arylalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester, or dialkylphosphate;

R^7 is H, alkyl, aryl, O-alkyl, O-aryl, cycloalkyl, O-cycloalkyl;

R^8 is hydrogen or alkyl;

R^3 is H, alkyl, cycloalkyl, aryl, O-alkyl, O-aryl; O-cycloalkyl;

R^4 is $\text{C}_1\text{-C}_5\text{-alkyl}$ or an unsaturated or saturated carbocycle selected from the group consisting of cyclopentyl, cyclohexyl, aryl;

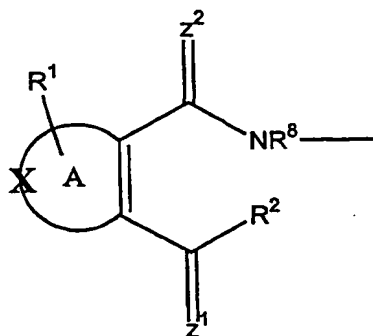
Z^1 and Z^2 are independent from each other O, S, NH or NR^5 ;

4

R^5 is OH, O-alkyl, O-aryl, alkyl or aryl;

Ar is a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

Y is hydrogen, halogen, CF_3 , OCF_3 , substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, Ar, O- substituted or unsubstituted Ar, O- substituted or unsubstituted alkylaryl, O- substituted or unsubstituted arylalkyl or



m is 0 or 1; and

q is 0 to 10,

with the proviso that when ring A is an unsubstituted carbocycle containing five carbon atoms and one double bond between the CZ^1 and CZ^2 -substituents, wherein $Z^1=Z^2=O$, and $R^2=OH$, the following compounds are excluded:

q=0; Y = hydrogen; Ar = phenylene or naphthylene, phenylene substituted with one or two chlorine atoms or with 2-methyl, 4-methyl, 4-methoxy, 4-ethoxy, 2, 6-diethyl, 2-chloro-4-methyl, 4-bromo, 4-cyano, 2,3-difluoro, 2,6-difluoro, 2,3,4-trifluoro;

q=0; Y= phenyl; Ar = phenylene;

q=1; m=1; $R^3=H$; Ar = phenylene; Y = 4-chloro-phenyl; D = O, S;

q=1; m=1; $R^3=H$; Ar = phenylene; Y = 4-phenyl; D = O.

The invention also provides a pharmaceutical composition comprising a compound of formula (I) including the compounds excluded by the disclaimer in claim 1, in free form or in the form of pharmaceutically acceptable salts and physiologically functional derivatives, together with a pharmaceutically acceptable diluent or carrier therefore.

The term "physiologically functional derivative" as used herein refers to compounds which are not pharmaceutical active themselves but which are transformed into their pharmaceutical active form in vivo, i.e. in the subject to which the compound is administered.

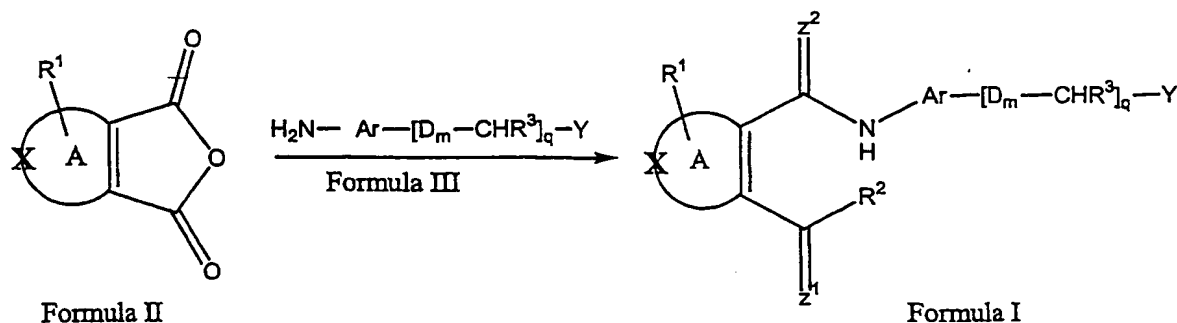
In another aspect, the present invention also provides a method for the treatment or prophylaxis of a condition where there is an advantage in inhibiting dihydroorotate dehydrogenase (DHODH) which comprises the administration of an effective amount of a compound of formula (I) and physiologically acceptable salts or physiologically functional derivatives thereof.

The invention is also directed to the use of compounds of the formula (I) and of their pharmacologically tolerable salts or physiologically functional derivatives for the production of a medicament for the prevention and treatment of diseases, where inhibition of the pyrimidine biosynthesis is of benefit.

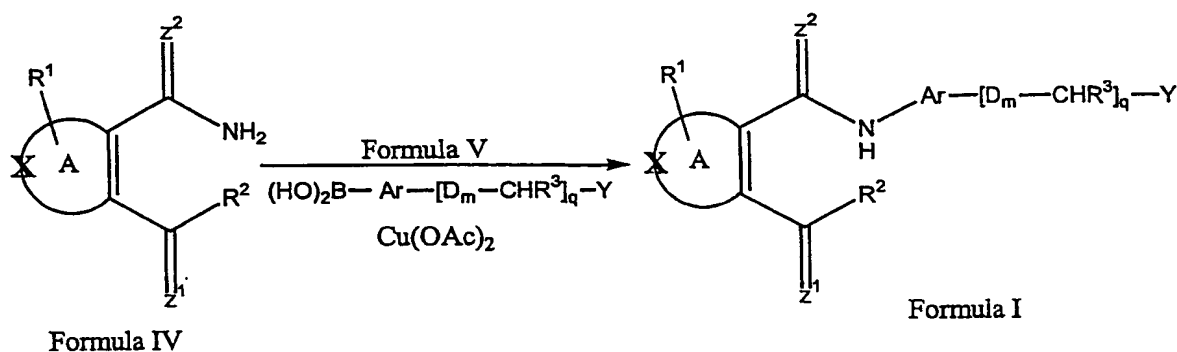
In addition, the present invention provides methods for preparing the desired amides of the formula (I).

A first method for synthesis of the amides of the formula (I) comprises the step of reacting an acid anhydride of formula (II) with an amine of the formula (III).

6



A second method of the invention for preparing the compounds of formula (I) comprises the step of reacting an amine of the formula (IV) with an arylboronic-acid of the general
 5 formula (V) $(\text{HO})_2\text{B}-\text{Ar}-[\text{D}_m-\text{CHR}^3]_q-\text{Y}$ [M. P. Winters, Tetrahedron Lett, 39, (1998), 2933-2936].



10 In the compounds of formula (I) the non-aromatic ring system A contains 4 to 8, preferably 5 or 6, and most preferred 5 carbon atoms. The ring system A comprises at least one double bond which is located between the CZ^1 and CZ^2 -substituents as depicted in
 15 Formula (I). In preferred embodiments, the compounds of the present invention contain only this double bond. In case of two or more double bonds, these double bonds are not-conjugated. One or more of the carbon atoms in the ring system A can be substituted by a group X, wherein X is selected from the group consisting of S, O, N, NH, NHR^4 , SO or SO_2 . In one preferred embodiment, none of the carbon atoms is substituted by a group X.

In the compounds of formula (I) D is O, S, SO_2 , NH, NHR^4 , or CH_2 .

20

D is preferably O, when $m = 1$.

In other preferred embodiments, m and q are zero and Y is hydrogen, F, CF₃, OCF₃, alkyl, alkyl substituted with halogen, phenyl or phenyl substituted with halogen, preferably F, CF₃, or OCF₃.

- 5 In the compounds of formula (I) R¹ is independently H, halogen, CF₃, OCF₃, or C₁-C₅-alkyl, preferably R¹ is H.

R² is H, OH, OR⁶, NH₂ or NHR³, preferably OH or OR⁶.

- 10 In preferred embodiments, R⁶ is benzoyloxymethyl, pivalyloxymethyl, isobutyryloxymethyl, 4-aminobutyryloxymethyl, butyryloxymethyl, 1-(butyryloxy)ethyl, 1-(butyryloxy)-2,2-dimethylpropyl, p-aminobenzoylmethyl, nicotinyloxymethyl, glutaryloxymethyl, 2-(2-methoxyethoxy)-acetyloxymethyl, [2-(2-methoxyethoxy)ethoxy]-acetyloxymethyl, 2-(morpholine-4-yl)-ethyl, diethylphosphonooxymethyl, 1-diethyl-
15 phosphonooxyethyl.

R³ is H, alkyl, aryl, O-alkyl or O-aryl, preferably H;

- R⁴ in formula (I) is C₁-C₅-alkyl or an unsaturated or saturated carbocycle selected from the
20 group consisting of cyclopentyl, cyclohexyl and aryl.

In formula (I) Z¹ and Z² are independent from each other O, S, NH or NR⁵, preferably both are O.

- 25 In formula (I) Ar is a monocyclic or polycyclic substituted or unsubstituted ring system which contains at least one aromatic ring and which may also contain one or more groups X selected from S, O, N, NH, NHR⁴, SO or SO₂. In preferred embodiments, Ar is a monocyclic aromatic ring or an aromatic bicyclic or tricyclic ring system. In case of substitutions of carbon atoms in the ring system, preferably one, two or three carbon atoms
30 are substituted by a group X as defined above.

The meaning of Ar includes carbocyclic aromatic groups such as phenyl, 1-naphthyl, 2-naphthyl, anthracenyl, in particular 1-anthracenyl and 2-anthracenyl, and

heterocyclic aromatic groups such as N-imidazolyl, 2-imidazolyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 2-pyranyl, 3-pyranyl, 4-pyranyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl and 5-oxazolyl. Ar includes also fused
5 polycyclic aromatic ring systems such as 9H-thioxanthene-10,10-dioxide in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other heteroaryl ring.

Suitable substituents of Ar are NO₂, CN, CO₂H, CONH₂, CONHR⁴, NH₂, NHR⁴, OH, O-R⁴, SH, SR⁴, halogenes (F, Cl, Br, I), alkyl CF₃, or OCF₃ (R⁴ = unsubstituted or
10 substituted alkyl, benzyl, carbocyclic or heterocyclic aromatics).

In formula (I) Ar is preferably phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl, whereby the aromatic groups may be substituted with nitro, F, I, CF₃, OCF₃ or phenyl or heteroaryl groups such as imidazolyl, thienyl, furanyl, pyridyl, pyrimidyl, pyranyl,
15 pyrazolyl, pyrazinyl, thiazolyl, oxazolyl, which in turn may substituted by the substituents given for Ar. Preferred substituents of the phenyl- or heteroaryl groups are Cl, F, I, CF₃, OCF₃ or alkyl.

In a preferred embodiment of the present invention Ar is substituted or unsubstituted
20 phenyl.

In particular preferred embodiments of the invention, q=0, Y is H or F, and Ar is phenyl which is either unsubstituted or substituted with F and/or CF₃ or OCF₃.

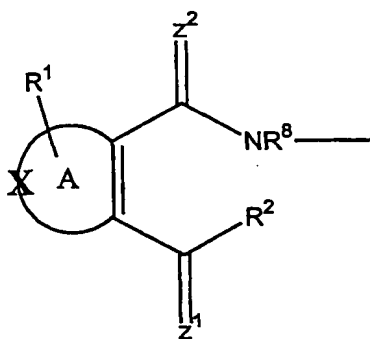
25 In another particularly preferred embodiment of the invention, q=0, and Ar and Y are substituted or unsubstituted phenylene and phenyl, respectively.

In further particularly preferred embodiments, D=O (thus m=1), R³ is H, q=1 or 2, Ar is phenylene which is either unsubstituted or substituted with F and/or CF₃ or OCF₃, and Y is
30 phenyl which is also either unsubstituted or substituted with F and/or CF₃ or OCF₃.

The compounds of the formula (I) to be used according to the invention can form salts with inorganic or organic acids or bases. Examples of such salts are, for example, alkali metal salts, in particular sodium and potassium salts, or ammonium salts.

- 5 Alkyl groups in the compounds of formula (I) can be straight-chain or branched, substituted or unsubstituted. This also applies if they occur in other groups, for example in alkoxy, alkylmercapto, alkoxycarbonyl or alkanoyl groups. Aryl groups in the compounds of formula (I) can be substituted or unsubstituted.
- 10 In formula (I) Y is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted Ar, substituted or unsubstituted O-Ar, substituted or unsubstituted O-alkylaryl, substituted or unsubstituted O-arylalkyl ; in case of said substitution, substitution of one or more hydrogen atoms of the alkyl-, cycloalkyl-, or aryl-groups by halogens are preferred. Y can also be

15



wherein A, X, R¹, R², R⁸, Z¹ and Z² have the meaning as defined above.

All halogens (F, Cl, Br, and I) can be used as substituent Y. F, CF₃ and OCF₃ are preferred.

20

In formula (I) q is 0 to 10, preferably q is 0, 1 or 2. If q is 1, m is preferably O.

The compounds of formula (I) may be obtained via various methods, including the method described in JP-A-50-121428. In preferred embodiments of the methods of the invention

25

the two following methods of synthesis are used.

Method 1: In a first step the cycloalkene-1,2-dicarboxylic acids can be obtained from the corresponding α,α' -dibromo alkanedicarboxylic acids as described by R.N. Mc Donald and R.R. Reitz, J. Org. Chem. 37, (1972) 2418. Cyclopentene-1,2-dicarboxylic acid can also be obtained in large amounts from pimelic acid [D.C. Owsley und J.J. Bloomfield, 5 Org. Prep. Proc. Int. 3, (1971) 61; A. Hassel and C.K. Ingold, J. Chem. Soc. (1926), 665].

Dicarboxylic acids substituted in or on the ring system can be synthesized in general via the cyanhydrine synthesis [Shwu-Jiüan Lee et.al. Bull. Inst. Chem. Academia Sinica Number 40, (1993), 1 or B. R. Baker at al., J. Org. Chem. 13, 1948, 123-133; and B. R. 10 Baker at al., J. Org. Chem. 12, 1947, 328-332].

The dicarboxylic acids can then be converted into the corresponding acid anhydrides by reacting them with acetic acid anhydride [P. Singh and S.M. Weinreb, Tetrahedron 32, (1976), 2379].

15

Other methods for preparing different acid anhydrides of formula (II) are described in V. A. Montero at al., J. Org. Chem. 54, (1989), 3664-3667; P. ten Haken, J. Heterocycl. Chem. 7, (1970), 1211-1213; K. Alder, H. Holzrichter, J. Lieb. Annalen d. Chem. 524, (1936), 145-180; K. Alder, E. Windemuth, J. Lieb. Annalen d. Chem. 543, (1940), 56-78; 20 and W. Flaig, J. Lieb. Annalen d. Chem. 568, (1950), 1-33.

These anhydrides may then be reacted with the corresponding amines to the desired amides of formula (I). This reaction can be carried out either by use of the reaction conditions as described in J.V. de Julian Ortiz et al., J. Med. Chem. 42, (1999), 3308 (designated route A 25 in Example 1) or by use of 4-dimethylamino pyridine (designated route B in Example 1).

30

Method 2: The amides of formula (I) can also be synthesized by reacting an amine of the formula (IV) with an arylboronic-acid of the general formula (V) [M. P. Winters, Tetrahedron Lett, 39, (1998), 2933-2936].

The compounds of the present invention can be used for a variety of human and animal diseases, preferably human diseases, where inhibition of the pyrimidine metabolism is beneficial. Such diseases are:

- fibrosis, uveitis, rhinitis, asthma or arthropathy, in particular, arthrosis
- all forms of rheumatism
- acute immunological events and disorders such as sepsis, septic shock, serious forms of allergy, graft versus host and host versus graft reactions. These immunological events also
- 5 include a desired modulation and suppression of the immune system
 - all types of autoimmune diseases, in particular rheumatoid arthritis, multiple sclerosis, insulin dependent diabetes mellitus and non-insulin dependent diabetes, and lupus erythematosus, ulcerative colitis, Morbus Crohn, psoriasis.
- 10 The class of compounds of the present invention is useful for the development of immunomodulatory and anti-inflammatory medicaments or, more generally, for the treatment of diseases where the inhibition of the pyrimidine biosynthesis is beneficial.
- The compounds of the present invention are also useful for the treatment of diseases which
- 15 are caused by malignant cell proliferation, such as all forms of cancer; in particular; e.g. lung cancer, leukemia, ovary cancer, sarcoma, Kaposi's sarcoma, cancer of the intestine, lymph node cancer, brain tumors, breast cancer, pancreas cancer, cancer of the prostate, skin cancer.
- 20 The compounds of the present invention can further be used for diseases that are caused by protozoal infestations in humans and animals. Such veterinary and human pathogenic protozoas are preferably intracellular active parasites of the phylum Apicomplexa or Sarcomastigophora, especially Trypanosoma, Plasmodia, Leishmania, Babesia and Theileria, Cryptosporidia, Sarcocystida, Amoebiasis, Coccidia and Trichomonads. These
- 25 active substances or corresponding drugs are especially suitable for the treatment of Malaria tropica, caused by *Plasmodium falciparum*, Malaria tertiana, caused by *Plasmodium vivax* or *Plasmodium ovale* and for the treatment of Malaria quartana, caused by *Plasmodium malariae*. They are also suitable for the treatment of Toxoplasmosis, caused by *Toxoplasma gondii*, Coccidiosis, caused for instance by *Isospora belli*, intestinal
- 30 Sarcosporidiosis, caused by *Sarcocystis suis hominis*, dysentery caused by *Entamoeba histolytica*, Cryptosporidiosis, caused by *Cryptosporidium parvum*, Chagas' disease, caused by *Trypanosoma cruzi*, sleeping sickness, caused by *Trypanosoma brucei rhodesiense* or *gambiense*, the cutaneous and visceral as well as other forms of

Leishmaniosis. They are also suitable for the treatment of animals infected by veterinary pathogenic protozoa, like *Theileria parva*, the pathogen causing bovine East coast fever, *Trypanosoma congolense congolense* or *Trypanosoma vivax vivax*, *Trypanosoma brucei brucei*, pathogens causing Nagana cattle disease in Africa, *Trypanosoma brucei evansi* causing Surra, *Babesia bigemina*, the pathogen causing Texas fever in cattle and buffalos, *Babesia bovis*, the pathogen causing european bovine Babesiosis as well as Babesiosis in dogs, cats and sheep, *Sarcocystis ovicanis* and *ovifelis* pathogens causing Sarcocystiosis in sheep, cattle and pigs, Cryptosporidia, pathogens causing Cryptosporidiosis in cattle and birds, Eimeria and Isospora species, pathogens causing Coccidiosis in rabbits, cattle, sheep, goats, pigs and birds, especially in chickens and turkeys. The use of the compounds of the present invention is preferred in particular for the treatment of Coccidiosis or Malaria infections, or for the preparation of a drug or feed stuff for the treatment of these diseases. This treatment can be prophylactic or curative. In the treatment of malaria, the compounds of the present invention may be combined with other anti-malaria agents.

The compounds of the present invention can further be used for viral infections or other infections caused for instance by *Pneumocystis carinii*.

The compounds of the formula (I) and their pharmacologically acceptable salts can be administered to animals, preferably to mammals, and in particular to humans, dogs and chickens as therapeutics per se, as mixtures with one another or in the form of pharmaceutical preparations which allow enteral or parenteral use and which as active constituent contain an effective dose of at least one compound of the formula I or a salt thereof, in addition to customary pharmaceutically innocuous excipients and additives. The compounds of formula (I) can also be administered in form of their salts, which are obtainable by reacting the respective compounds with physiologically acceptable acids and bases.

The therapeutics can be administered orally, e.g. in the form of pills, tablets, coated tablets, sugar coated tablets, hard and soft gelatin capsules, solutions, syrups, emulsions or suspensions or as aerosol mixtures. Administration, however, can also be carried out rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injections or infusions, or percutaneously, e.g. in the form of ointments, creams or tinctures.

In addition to the active compounds of formula (I), the pharmaceutical composition can contain further customary, usually inert carrier materials or excipients. Thus, the pharmaceutical preparations can also contain additives, such as, for example, fillers, extenders, disintegrants, binders, glidants, wetting agents, stabilizers, emulsifiers, preservatives, sweetening agents, colorants, flavorings or aromatizers, buffer substances, and furthermore solvents or solubilizers or agents for achieving a depot effect, as well as salts for changing the osmotic pressure, coating agents or antioxidants. They can also contain two or more compounds of the formula (I) or their pharmacologically acceptable salts and also other therapeutically active substances.

Thus, the compounds of the present invention can be used in the form of one substance alone or in combination with other active compounds – for example with medicaments already known for the treatment of the aforementioned diseases, whereby in the latter case a favorable additive, amplifying effect is noticed. Suitable amounts to be administered to humans range from 5 to 500 mg.

To prepare the pharmaceutical preparations, pharmaceutically inert inorganic or organic excipients can be used. To prepare pills, tablets, coated tablets and hard gelatin capsules, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts, etc. can be used. Excipients for soft gelatin capsules and suppositories are, for example, fats, waxes, semi-solid and liquid polyols, natural or hardened oils etc. Suitable excipients for the production of solutions and syrups are, for example, water, sucrose, invert sugar, glucose, polyols etc. Suitable excipients for the production of injection solutions are, for example, water, alcohols, glycerol, polyols or vegetable oils.

The dose can vary within wide limits and is to be suited to the individual conditions in each individual case. For the above uses the appropriate dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, however, satisfactory results are achieved at dosage rates of about 1 to 100 mg/kg animal body weight preferably 1 to 50 mg/kg. Suitable dosage rates for larger mammals, for example humans, are of the order of from about 10 mg to 3 g/day, conveniently administered once, in divided doses 2 to 4 times a day, or in sustained release form.

In general, a daily dose of approximately 10 mg to 5000 mg, preferably 50 to 500 mg, per human individual is appropriate in the case of the oral administration which is the preferred form of administration according to the invention. In the case of other administration forms too, the daily dose is in similar ranges.

The compounds of formula (I) can also be used in the form of a precursor (prodrug) or a suitably modified form, that releases the active compound *in vivo*. Such precursors such as the preferred embodiments of R⁶ can be obtained for example by masking the free acid group with an ester group, which is then in turn transformed into the free acid group *in vivo* [F. W. Sum et. al. Bioorg. & med. Chem. Lett. 9 (1999), 1921; Ada Rephaeli et. al. Drug Development Research 50 (2000) 379 ; Current Med. Chem. Vol 6 (1999), 593]. Also such precursors for the preferred embodiments of R⁵ can be obtained for example by masking the amidine with an hydroxy group, which is then in turn transformed into the free amidine *in vivo* [R.M. Scarborough, J. Med. Chem. 43, 19, (2000), 3454-3473].

The following examples show examples for the synthesis of the compounds of the present invention and demonstrate their DHODH inhibiting effect.

20 Examples

1. Synthesis of compounds of formula (I)

The compounds of formula (I) were obtained through synthesis route (A) or (B). The amines were purchased from Sigma-Aldrich Chemie GmbH, Grünwalder Weg 30, D-82041 Deisenhofen.

Synthesis Route (A):

A solution of the corresponding amine (1 equivalent) was added slowly to a solution of the dicarboxylic acid (1 equivalent) in toluene at 60°C. The mixture was stirred at this temperature for 1h, then cooled to room temperature and filtrated. The precipitate was washed with 2 M HCl and then recrystallized from ethanol/water (1:1). The amide thus obtained was characterized by HPLC-mass spectroscopy.

Synthesis Route (B):

A solution of the corresponding amine (1 equivalent) in dry dichloromethane was added slowly to a solution of the dicarboxylic acid anhydride (1 equivalent) and 4-dimethylamino pyridine (1 equivalent) in dry dichloromethane at ambient temperature. After 16 hours, the mixture was concentrated. The residue was taken up in ethyl acetate and the organic phase was washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was the corresponding amide which was characterized by HPLC-mass spectroscopy.

Compounds 1 and 2 were synthesized, as described in method A and B. All other compounds were synthesized, as described in method B. Compound 2 was further characterized by ¹H-NMR.

15 Synthesis of 2-(4-Benzoyloxy-phenylcarbamoyl)-cyclopent-1-enecarboxylic acid
 (Compound 1) (Synthesis Route A)

A solution of 117 mg (0.5 mmol) 4-Benzoyloxyphenylamine-hydrochloride in 1 ml of toluene was added slowly to a solution of 69 mg (0.5 mmol) 5,6-Dihydro-4*H*-cyclopenta[c]furan-1,3-dione in 2 ml of toluene at 60°C. The mixture was stirred at this temperature for 1h, then cooled to room temperature and filtrated. The precipitate was washed with 2 M HCl and then recrystallized from ethanol/water (1:1) yielding 158 mg (85%) of the product.

25 Synthesis of 2-(Biphenyl-4-ylcarbamoyl)-cyclopent-1-enecarboxylic acid
 (Compound 2) (Synthesis Route A)

A solution of 8.6 g (51 mmol) Biphenyl-4-amine in 50 ml of toluene was added slowly to a solution of 7.0 g (51 mmol) 5,6-Dihydro-4*H*-cyclopenta[c]furan-1,3-dione in 50 ml of toluene at 60°C. The mixture was stirred at this temperature for 1h, then cooled to room temperature and filtrated. The precipitate was washed with 2 M HCl and then recrystallized from ethanol/water (1:1) yielding 14 g (91%) of the product.

¹H-NMR: (300 MHz, d₆-DMSO) δ = 1.93 (quin, J=7.52 Hz 2H,CH₂), 2.66 (t, J= 7.52 Hz, 2H, CH₂), 2.79 (t, J=7.52 Hz, 2H,CH₂), 7.33 (m, 1H,CH_{ar}), 7.45 (m,1H,CH_{ar}), 7.64 (m, 1H, CH_{ar}), 7.72 (d, J=8.73 Hz, 2H, CH_{ar}), 10.34 (s, 1H, NH).

5 2. Inhibition Assay of DHODH activity

The standard assay mixture contained 50 μ M decyclo ubichinone, 100 μ M dihydroorotate, 60 μ M 2,6-dichloroindophenol, as well as 20 mU DHODH. The volume activity of the recombinant enzyme used was 30 U/ml. Measurements were conducted in 50 mM TrisHCl
10 (150 mM KCl, 0,1% Triton X-100, pH 8,0) at 30°C in a final volume of 1 ml. The components were mixed, and the reaction was started by adding dihydroorotate. The course of reaction was followed by spectrophotometrically measuring the decrease in absorption at 600 nm for 2 min.

15 Inhibitory studies were conducted in a standard assay with additional variable amounts of inhibitor. For the determination of the IC₅₀ values (concentration of inhibitor required for 50% inhibition) at least five different inhibitor concentrations were applied.

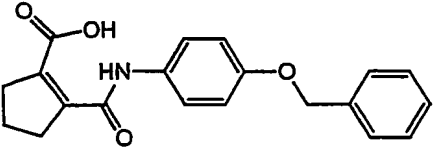
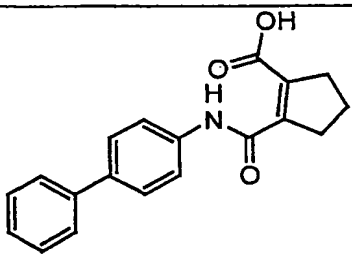
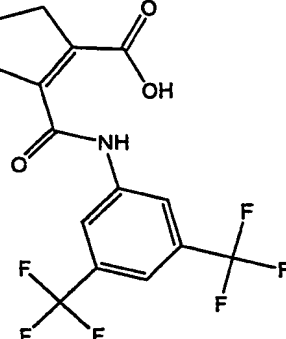
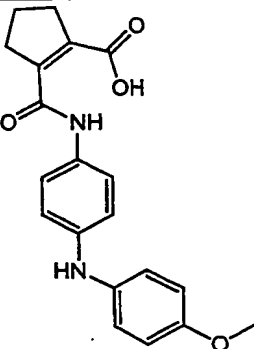
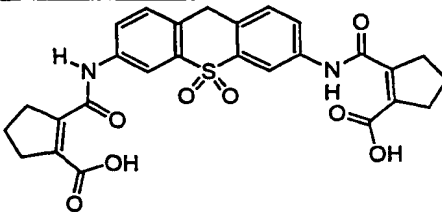
These investigations were carried out with recombinant human as well as with recombinant
20 murine DHODH provided by Prof. M. Löffler, Marburg, Germany [M. Löffler, Chem. Biol. Interact. 124, (2000), 61-76].

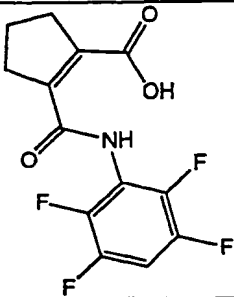
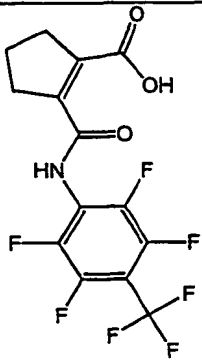
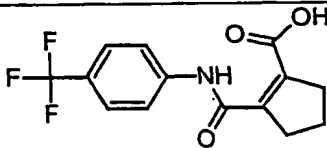
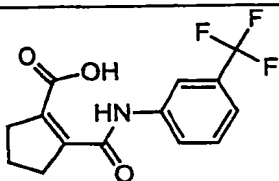
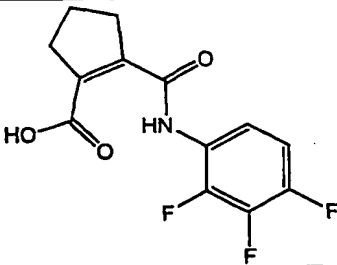
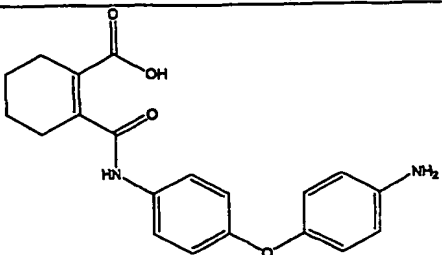
As a reference the active metabolite of leflunomide A77-1726 (Compound 12) was used [J. Jöckel et. al. Biochemical Pharmacology 56 (1998), 1053].

25

The results of the inhibition assay are shown in the following Table 1. It is evident from the comparison of the IC₅₀-values that the compounds used in the present invention not only have a comparable or even better inhibitory activity on the human enzyme than the active metabolite of leflunomide but also a higher specificity for the human enzyme.

Table 1

N	Formula	HPLC/MS (ESI)	Molecular Mass [g/mol]	IC ₅₀ -Value [μmol]	
				Mouse Enzyme	Human Enzyme
1		338 [M+H] ⁺ 336 [M-H] ⁺	337,37	8,2	0,350
2		306 [M-H] ⁺	307,35	4	0,690
3		366 [M-H] ⁺	367,24	N.D.	1,0
4		353 [M+H] ⁺ 351 [M-H] ⁺	352,39	Weakly active	1,0
5		537 [M+H] ⁺ 535 [M-H] ⁺	536,55	Weakly active	1,1

6		302 [M-H] ⁺	303,21	N.D.	1,3
7		370 [M-H] ⁺	371,21	N.D.	1,6
8		300 [M+H] ⁺ 298 [M-H] ⁺	299,25	0,93	1,6
9		300 [M+H] ⁺ 298 [M-H] ⁺	299,25	55	6,8
10		286 [M+H] ⁺ 284 [M-H] ⁺	285,22	N.D.	6,8
11		353 [M+H] ⁺ 351 [M-H] ⁺	352,38	N.D.	7,0

12			272,22	0,20	0,67
----	-----------------------------------------------------------------------------------	--	--------	------	------

N.D. = not determined

3. Proliferation assay of human T-cells

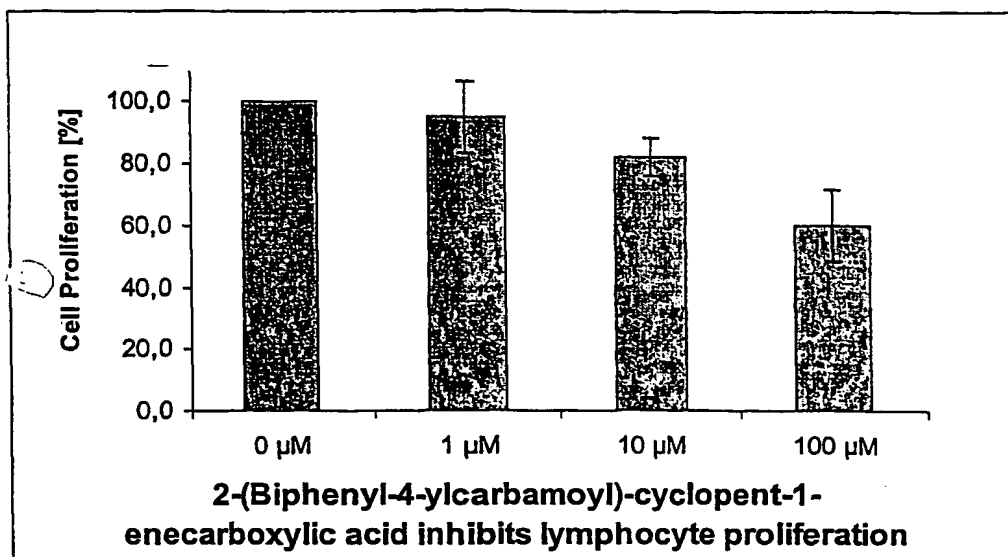
5

Buffy coats of healthy donors were obtained from the local Red Cross; from these human mononuclear cells (MNC) were isolated using Accuspin™ System-Histopaque-1077 (Sigma) according to the protocol recommended by the manufacturer. Cells were seeded at densities of 5×10^4 or 1×10^5 cells per well in 96 well flat bottom plates in RPMI 1640 supplemented with 10% fetal calf serum, 2 mM L-glutamine and penicillin/streptomycin. Cells were activated with 1 $\mu\text{g/ml}$ phytohaemagglutinin (PHA, Sigma) or 20 nM PMA (phorbol-12-myristate-13-acetate)/ 10 μM ionomycin (Calbiochem) and incubated with the test compounds in a final volume of 100 μl for 48 hours. Proliferation was measured using the CellTiter 96® Aqueous One Solution Cell Proliferation Assay (Promega) according to the lymphocyte assay protocol supplied by the manufacturer.

15

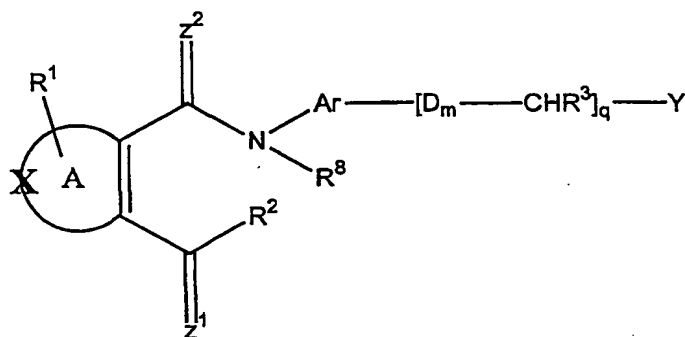
2-(Biphenyl-4-ylcarbamoyl)-cyclopent-1-enecarboxylic acid (100 μM) caused a reduction of human lymphocyte cell proliferation of 40% indicating that the compound has an inhibitory effect on DHODH in vivo.

20



CLAIMS:

1. Compounds of the general formula (I)



wherein

A is a non-aromatic ring system containing 4 to 8 carbon atoms, wherein the ring system comprises at least one double bond and wherein one or more of the carbon atoms in the ring can be substituted by a group X, wherein X is selected from the group consisting of S, O, N, NH, NHR⁴, SO or SO₂, and wherein one or more of the carbon atoms of the ring can carry a substituent R¹

D is O, S, SO₂, NH, NHR⁴, or CH₂,

R¹ is independently H, halogen, CF₃, OCF₃, or C₁-C₅-alkyl;

R² is H, OH, OR⁶, NH₂, NHR⁷;

R⁶ is H, alkyl, cycloalkyl, aryl, arylalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester, dialkylphosphate;

R⁷ is H, alkyl, aryl, O-alkyl, O-aryl, cycloalkyl or O-cycloalkyl;

R⁸ is hydrogen or alkyl;

25

R³ is H, alkyl, cycloalkyl, aryl, O-alkyl, O-aryl or O-cycloalkyl;

R^4 is C_1 - C_5 -alkyl or an unsaturated or saturated carbocycle selected from the group consisting of cyclopentyl, cyclohexyl or aryl;

Z^1 and Z^2 are independent from each other O, S, NH or NR^5 ;

5

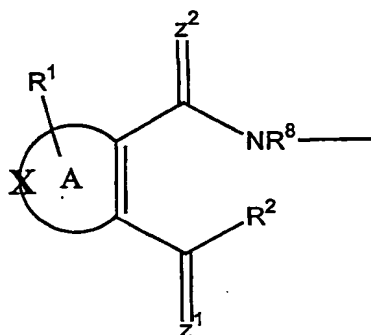
R^5 is OH, O-alkyl, O-aryl, alkyl or aryl ;

10

Ar is a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

15

Y is hydrogen, halogen, CF_3 , OCF_3 , substituted or unsubstituted alkyl substituted or unsubstituted cycloalkyl, Ar, O- substituted or unsubstituted Ar, O- substituted or unsubstituted alkylaryl, O- substituted or unsubstituted arylalkyl or



20

m is 0 or 1; and

q is 0 to 10,

25

with the proviso that when ring A is an unsubstituted carbocycle containing five carbon atoms and one double bond between the CZ^1 and CZ^2 -substituents with $Z^1=Z^2=O$ and $R^2=OH$, the following compounds are excluded:

$q=0$; Y = hydrogen; Ar = phenylene or naphthylene, phenylene substituted with one or two chlorine atoms or with 2-methyl, 4-methyl, 4-methoxy, 4-ethoxy, 2, 6-diethyl, 2-chloro-4-methyl, 4-bromo, 4-cyano, 2,3-difluoro, 2,6-difluoro, 2,3,4-trifluoro;

5 $q=0$; Y = phenyl; Ar = phenylene;

$q=1$; $m=1$; $R^3=H$; Ar = phenylene; Y = 4-chloro-phenyl; D = O, S;

$q=1$; $m=1$; $R^3=H$; Ar = phenylene; Y = 4-phenyl; D = O.

10

2. A compound of claim 1, wherein Z^1 and Z^2 are both O.

3. A compound of claim 1 or 2, wherein the ring system A contains 5 or 6 carbon atoms.

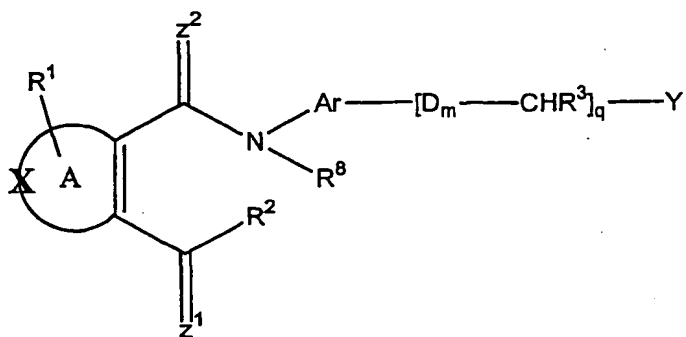
15

4. A compound of any of claims 1 to 3, wherein Ar is phenyl, 1-naphthyl, 2-naphthyl, 2-naphthyl, 1-anthracenyl and 2-anthracenyl or 9H-thioxanthene-10,10-dioxide.

5. A compound of any of claims 1 to 4, wherein R^2 is OH or OR^6 .

20

6. A pharmaceutical composition comprising a compound of the general formula (I)



wherein

25

A is a non-aromatic ring system containing 4 to 8 carbon atoms, wherein the ring system comprises at least one double bond and wherein one or more of

the carbon atoms in the ring can be substituted by a group X, wherein X is selected from the group consisting of S, O, N, NH, NHR⁴, SO or SO₂, and wherein one or more of the carbon atoms of the ring can carry a substituent R¹

5

D is O, S, SO₂, NH, NHR⁴, or CH₂,

R¹ is independently H, halogen, CF₃, OCF₃ or C₁-C₅-alkyl;

10

R² is H, OH, OR⁶, NH₂, NHR⁷;

R⁶ is H, alkyl, cycloalkyl, aryl, arylalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester, dialkylphosphate;

R⁷ is H, alkyl, aryl, O-alkyl, O-aryl, cycloalkyl or O-cycloalkyl;

15

R⁸ is hydrogen or alkyl;

R³ is H, alkyl, cycloalkyl, aryl, O-alkyl, O-aryl or O-cycloalkyl;

R⁴ is C₁-C₅-alkyl or an unsaturated or saturated carbocycle selected from the group consisting of cyclopentyl, cyclohexyl, aryl;

20

Z¹ and Z² are independent from each other O, S, NH or NR⁵ ;

R⁵ is OH, O-alkyl, O-aryl, alkyl or aryl ;

25

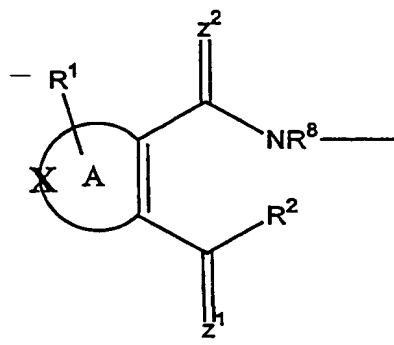
Ar is a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

Y is hydrogen, halogen, CF₃, OCF₃, substituted or unsubstituted alkyl

30

substituted or unsubstituted cycloalkyl, Ar, O- substituted or unsubstituted Ar, O- substituted or unsubstituted alkylaryl, O- substituted or unsubstituted arylalkyl or

25



R^8 is hydrogen or alkyl;

m is 0 or 1; and

q is 0 to 10,

in free form or in the form of pharmaceutically acceptable salts and physiologically functional derivatives, together with pharmaceutically acceptable diluents or carriers.

7. Method for the treatment or prophylaxis of a condition where there is an advantage in inhibiting dihydroorotate dehydrogenase (DHODH) which comprises the administration of an effective amount of a compound of formula (I) as defined in any of claims 1 to 5, including the compounds excluded in claim 1 and physiologically acceptable salts and physiologically functional derivatives thereof.

8. Use of the compounds of the formula (I) as defined in any of claims 1 to 5, including the compounds excluded in claim 1, and physiologically functional derivatives and of their pharmacologically tolerable salts in the manufacture of a medicament for use in treatment of a disease or a therapeutic indication in which inhibition of dihydroorotate dehydrogenase is beneficial.

9. Use of claim 8 wherein the disease or indication is selected from the group consisting of rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are

caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma or athropathy.

10. A process for the preparation of a compound of formula I which process comprises
5 the step of reacting an acid anhydrid of formula (II) with an amine of formula (III)
or an amine of formula (IV) with a boronic acid of formula (V).

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 01/07948

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C233/60 C07C233/58 C07C233/59 C07C233/62 C07D335/12
 A61K31/185 A61P35/00 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 33 46 814 A (EISAI CO LTD) 28 June 1984 (1984-06-28) page 23 -page 24; claims	1-10
A	DE JULIAN-ORTIZ, JESUS V. ET AL: "Virtual Combinatorial Syntheses and Computational Screening of New Potential Anti-Herpes Compounds" JOURNAL OF MEDICINAL CHEMISTRY (1999), 42(17), 3308-3314 , 1999, XP002199074 cited in the application page 3312 -page 3313 --- -/--	1-10

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the International filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the International filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the International search

16 May 2002

Date of mailing of the International search report

31/05/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Sánchez García, J.M.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/07948

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CHEMICAL ABSTRACTS, vol. 84, no. 5, 2 February 1976 (1976-02-02) Columbus, Ohio, US; abstract no. 26881, MATSUI, KAZUO ET AL: "N-Substituted-.DELTA.-cyclopentene-1,2-d icarboxylic acid monoamides as herbicides" XP002199075 abstract & JP 50 121428 A (MITSUBISHI CHEMICAL INDUSTRIES CO., LTD., JAPAN) 23 September 1975 (1975-09-23) cited in the application</p>	1-5,10
A	<p>CHEMICAL ABSTRACTS, vol. 94, no. 25, 22 June 1981 (1981-06-22) Columbus, Ohio, US; abstract no. 208514, TAKEDA CHEMICAL INDUSTRIES, LTD., JAPAN: "Tetrahydrophthalamide derivatives" XP002199076 abstract & JP 55 157547 A (TAKEDA CHEMICAL INDUSTRIES, LTD., JAPAN) 8 December 1980 (1980-12-08)</p>	1-5,10
A	<p>DE 28 51 379 A (TAKEDA CHEMICAL INDUSTRIES LTD) 31 May 1979 (1979-05-31) page 22 -page 36; claims</p>	1-5,10
A	<p>EP 0 097 056 A (NIPPON KAYAKU KK) 28 December 1983 (1983-12-28) claims</p>	1-5,10
A	<p>DE 29 21 002 A (MITSUBISHI CHEM IND) 29 November 1979 (1979-11-29) claims</p>	1-5,10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/07948

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 3346814	A	28-06-1984	JP 1036819 B 02-08-1989
			JP 1551911 C 23-03-1990
			JP 59118750 A 09-07-1984
			AU 2253183 A 05-07-1984
			BE 898570 A1 27-06-1984
			CA 1202312 A1 25-03-1986
			CH 656875 A5 31-07-1986
			DE 3346814 A1 28-06-1984
			DK 596083 A 28-06-1984
			ES 528409 D0 01-11-1985
			ES 8601859 A1 01-03-1986
			ES 543810 D0 16-06-1986
			ES 8608486 A1 01-12-1986
			FR 2538386 A1 29-06-1984
			GB 2133006 A ,B 18-07-1984
			HU 189799 B 28-07-1986
			IT 1170275 B 03-06-1987
			NL 8304406 A 16-07-1984
			PH 19459 A 18-04-1986
			SE 8307119 A 28-06-1984
			US 4661630 A 28-04-1987
			ZA 8309546 A 29-08-1984
JP 50121428	A	23-09-1975	NONE
JP 55157547	A	08-12-1980	NONE
DE 2851379	A	31-05-1979	JP 55059153 A 02-05-1980
			JP 1312828 C 28-04-1986
			JP 54076557 A 19-06-1979
			JP 60023668 B 08-06-1985
			CH 636345 A5 31-05-1983
			DE 2851379 A1 31-05-1979
			FR 2409983 A1 22-06-1979
			GB 2009150 A ,B 13-06-1979
			IL 56012 A 31-07-1983
			US 4328367 A 04-05-1982
			BR 7807798 A 31-07-1979
EP 0097056	A	28-12-1983	JP 59172446 A 29-09-1984
			JP 58219104 A 20-12-1983
			AU 1526483 A 22-12-1983
			BR 8303127 A 31-01-1984
			EP 0097056 A2 28-12-1983
DE 2921002	A	29-11-1979	JP 54154737 A 06-12-1979
			BR 7903257 A 11-12-1979
			DE 2921002 A1 29-11-1979
			FR 2426674 A1 21-12-1979
			GB 2023137 A 28-12-1979
			IT 1115243 B 03-02-1986